A Transcatheter Intracardiac Shunt Device for Heart Failure with Preserved Ejection Fraction

Gerd Hasenfuβ, MD, Chris Hayward MD, Dan Burkhoff, MD, Frank E. Silvestry, MD, Scott McKenzie, MD, Filip Malek, MD, Jan Van der Heyden, MD, Professor Irene Lang, MD, Professor Mark C Petrie, MD, Professor John GF Cleland, MD, Professor Martin Leon, MD and Professor David M Kaye MD*****, on behalf of the **REDUCE LAP-HF** study investigators. *****Corresponding author.

Affiliations/Title (Full Professors):
Professor Gerd Hasenfuβ, MD, Georg-August Universität, Gottingen, Germany;
Professor Chris Hayward MD, St Vincent Hospital, Sydney, Australia;
Dan Burkhoff, MD, MD, PhD, Columbia University, New York, NY, USA;
Frank Silvestry, MD, Hospital of the University of Pennsylvania, Philadelphia PA, USA;
Scott McKenzie, MD, The Prince Charles Hospital, Brisbane, Australia
Filip Malek, MD, Na Homolce Hospital, Prague, Czech Republic
Jan Van der Heyden, MD, St Antonius Ziekenhuis, Nieuwegein, The Netherlands
Professor Irene Lang, MD, Allgemeines Krankenhaus Universitätskliniken, Vienna, Austria
Mark C Petrie, MD, Golden Jubilee National Hospital, Glasgow, Scotland, Great Britain;
Professor John GF Cleland, MD, National Heart & Lung Institute, Royal Brompton and Harefield Hospitals, Imperial College, London, Great Britain;
Professor Martin Leon, MD, Columbia University Medical Center, New York, NY, USA;
Professor David Kaye, MD, Alfred Hospital and Baker IDI Heart & Diabetes Institute Melbourne.

Address for Correspondence
Professor David M Kaye
Dept. of Cardiology
Alfred Hospital
Commercial Rd
Melbourne 3004
Victoria
Australia
Tel + 61 3 9076 3263
Email david.kaye@bakeridi.edu.au

Abstract (250 words)

Background: Heart failure with preserved ejection fraction (HFPEF) is common but no treatment has yet been shown to improve symptoms or prognosis. The pathophysiology of HFPEF is complex but characterized by increased left atrial pressure, especially during exertion, which may be a key therapeutic target.

Methods: The REDUCE LAP-HF (REDUCe Elevated Left Atrial Pressure in Patients with Heart Failure) study was an open-label single arm study designed to evaluate the performance and safety of a trans-catheter inter-atrial shunt device (IASD, Corvia Medical) in patients with symptoms of HFPEF despite pharmacological therapy, LVEF>40%, and an elevated pulmonary capillary wedge pressure (PCWP) at rest (>15mmHg) or during exercise (>25mmHg). The primary objectives were to assess device safety and performance at six months, together with measures of clinical efficacy, including functional capacity and clinical status.

Findings: IASD placement was successful in 64 patients (mean age 69±8years; 66% women; median [IQR] NT-proBNP 377 [222-925] pg/ml) and appeared safe and well tolerated. Sustained device patency was confirmed by left-to-right shunting (pulmonary/systemic flow: 1.06±0.32 baseline; 1.27±0.20 at 6 months; p=0.0004). Exercise PCWP was lower at 6 months at 20 watts (32±8 vs 29±9; p=0.0124) and peak (34±8 vs32±8; p=0.0255) despite increased exercise duration (7.3±3.1 vs 8.2±3.4 minutes, p=0.03). Minnesota quality of life scores (49±20 vs 36±23, p<0.0001) and 6 minute walk distance (313±105 vs 345±106 metres (p=0.0023) had improved by six months.

Interpretation: Implantation of an interatrial shunt device is feasible, appears safe, reduces left atrial pressure during exercise and may be a novel strategy for the management of HFPEF. The effectiveness of IASD compared to current therapy for patients with HFPEF requires validation in a randomized controlled trial.

Funding: Corvia Medical Inc. (Formerly DC Devices Inc.)

Introduction

Many patients with symptoms of heart failure do not have evidence of reduced left ventricular systolic function; a syndrome which has been termed heart failure with preserved ejection fraction (HFPEF) [1,2] to distinguish it from those with heart failure and a reduced ejection fraction (HFREF). Epidemiological studies suggest that the incidence of HFPEF is rising [3,4], although it is unclear whether this is primarily due to improved recognition, the presence of an aging population or increases in the prevalence of co-morbid diseases such as hypertension, chronic kidney disease and diabetes; each likely making a contribution.

Whilst pharmacological treatment has improved symptoms and reduced morbidity and mortality for patients with HFREF, finding an effective treatment for patients with HFPEF has proved elusive [5-10]. The hallmark of HFPEF is effort intolerance which is associated with a profound and rapid increase in left atrial pressure during exercise reflecting impaired left ventricular diastolic reserve[11,12], with consequent pulmonary congestion. This disproportionate rise in left atrial pressure is thought to provoke symptoms and contribute to increased morbidity and mortality in HFPEF [13].

In 1916, Lutembacher described the combination of mitral stenosis, which mimics some of the pathophysiology of HFPEF, and an atrial septal defect (ASD). Patients with Lutembacher's syndrome may have fewer symptoms and better outcomes compared with patients with pure mitral stenosis and closure of their ASD may cause a rise in pulmonary artery pressure and pulmonary oedema in some patients. An iatrogenic left to right atrial shunt is thus a potentially attractive intervention which might have therapeutic value. Haemodynamic modelling based upon clinical measurements suggests that an appropriately-sized iatrogenic ASD could attenuate exercise induced increases in left atrial pressure in patients with HFPEF [14]. We postulated that a novel device-based therapy targeting a common pathophysiologic feature of HFPEF might succeed where pharmacological therapies have failed. The REDUCE LAP-HF study (REDUCe Elevated Left Atrial Pressure in Patients with Heart Failure) was designed to evaluate the device performance and safety of a trans-catheter, transvenous inter-atrial shunt device (IASD, Corvia Medical Inc.) in symptomatic patients with HFPEF.

Methods

Study Design

The study was a multi-centre prospective, non-randomized, open label, single-arm study designed to investigate the safety and performance of a trans-catheter interatrial shunt device (IASD system II, Figure 1). The study design has been described in detail elsewhere [15] (clin.trials.gov #: NCT01913613).

Patient population

Patients with known HFPEF were eligible for study inclusion if they had evidence of chronic symptomatic HF (NYHA class II-IV), a left ventricular ejection fraction >40% and an elevated pulmonary capillary wedge pressure (PCWP) at rest (>15mmHg) or during exercise (>25mmHg) measured by right heart catheterization. Patients with significant right ventricular dysfunction including a central venous pressure (CVP) >14 mmHg and tricuspid annular plane systolic excursion (TAPSE) <14 mm were excluded.

Cardiac catheterization and device implantation

All patients underwent right heart catheterization with assessment of cardiac output and central haemodynamics (right atrial pressure, pulmonary artery pressure and PCWP) at rest and during supine bicycle exercise before (during a separate screening evaluation) and 6 months after device implantation. Following baseline haemodynamic measurements, symptom-limited supine bicycle exercise commenced at 20 Watts (W) with 20W increments every 3 minutes until the patient achieved maximum effort. Blood samples were collected from the pulmonary artery and vena cavae at baseline and follow-up study to measure oxygen saturation and to evaluate left to right shunting as reflected by the Q_p:Q_s ratio. Device insertion was conducted within 45 days of screening. Implantation was performed percutaneously via the femoral vein on a separate occasion[16]. Standard trans-septal puncture of the interatrial septum was performed using the operator's preferred technique including fluoroscopy and transoesophageal or intra-cardiac echocardiography and the device was positioned using an "over the wire technique". Patients not taking oral anticoagulants were treated with aspirin (75 – 325 mg daily) indefinitely, and clopidogrel (75 mg daily) for 6 months. Patients treated with oral

anticoagulants continued on oral anticoagulants after the procedure. Endocarditis prophylaxis was advised for a minimum of 6 months post implant.

Device performance, safety and efficacy end points at follow-up

The primary objectives of the study were to assess device performance and safety. The study sample size was calculated as that required to demonstrate a device and procedure safety profile to other comparable procedures[15] . The primary device performance end-points were defined as the proportion of patients with successful device implantation, the percentage of patients with a reduction in PCWP at 6 months either at rest or during exercise compared to baseline, and the presence of persistent left to right trans-device blood flow at 6 months. The primary safety end-points were peri-procedural and 6 month major adverse cardiac and cerebrovascular events (MACCE) defined as death, stroke, myocardial infarction or a systemic embolic event (excluding pulmonary thromboembolism), or need for cardiac surgical device removal within 6 months. Echocardiograms performed at the implanting site per protocol were analysed at an independent core laboratory. Secondary outcome measures included the incidence of major adverse events, heart failure hospitalization over the entire study together with changes in echocardiographic parameters, functional capacity (6 minute walk), natriuretic peptides and quality of life assessments (Minnesota Living with Heart Failure Questionnaire, MLWHFQ). All patients gave written informed consent and the protocol was approved by each institutional ethics committee, and competent authorities.

Statistical methods

Normally distributed data are presented as mean ± standard deviation and non-parametric data as median and interquartile range. As appropriate a paired t test or Wilcoxon matched pairs sign-rank test were used to compare follow-up to baseline data. The null hypothesis was rejected at $p<0.05$.

Role of the funding source

The study was funded by Corvia Medical Incorporated. Data collection and analysis was performed by Medpass International Limited, Windsor House, Worcestershire, United Kingdom. Interpretation of the results and preparation of the manuscript was the responsibility of the steering committee and principal investigators. Corvia played no role in the collection, analysis, interpretation of data or the

decision to submit the manuscript. All study authors reviewed the manuscript and endorsed its submission.

Results

Study population characteristics

Of 102 patients enrolled from 21 centres, 68 met the inclusion and exclusion criteria. The commonest reasons for exclusion were failure to meet the haemodynamic inclusion criteria (PCWP too low in 22, and CVP too high in 3 patients). One patient was excluded for each of the following reasons: LVEF< 40%; cardiac index < 2.0 L/min/m^2; renal impairment; cerebrovascular disease; tricuspid regurgitation; mitral regurgitation; coronary disease; elevated pulmonary vascular resistance; and pneumonia. Two patients withdrew after qualification. Implantation of the IASD system was abandoned in two patients and was successful in 64. The baseline demographics of those implanted are shown in Table 1. Consistent with the HFPEF phenotype, the PCWP increased during exercise from 18±5 to 35±8 mmHg (p<0.0001), the mean pulmonary pressure rose from 25±7 to 44±9 mmHg (p<0.0001) and the mean right atrial pressure increased from 9±4 to 18±5 mmHg (p<0.0001). The cardiac output rose from 5.6±1.7 to 8.4±2.7 L/min (p<0.0001). The mean exercise time during haemodynamic testing was 7.3±3.1 minutes at a workload of 43±18 Watts.

Primary safety end point

No patient experienced a peri-procedural or major adverse cardiac or cerebrovascular event (MACCE), including death, stroke, myocardial infarction, pulmonary or systemic embolism or need for cardiac surgical intervention for device related complications, during six months follow-up. One patient declined a final clinical follow-up due to non-cardiovascular illness.

Primary device performance end points

The implant procedure was not completed due to a trans-septal puncture complication without further sequelae in one patient, and perceived unsuitable atrial septal anatomy in another. In three patients the initial device was removed due to unsuitable position (n=2) or a suspected small mobile thrombus in the right atrium (n=1) with a second device deployed in all three without incident. Sixty patients underwent right heart catheterisation for haemodynamic evaluation at 6 months, and exercise haemodynamic responses were evaluated in 59 patients. At follow-up, 42 patients (71%) met the primary device performance definition of a reduction in PCWP either at rest or during exertion as compared to their baseline values (n = 37). Of these patients, 52% (31/60) had a reduction in PCWP

at rest, 58% 34/59) had a lower PCWP during exertion and 39% (23/59) fulfilled both criteria. All patients with adequate echocardiographic image quality (n=50), had evidence of left to right flow through the device by colour flow Doppler flow at 6 months. Right to left flow by colour flow Doppler was not observed. Haemodynamic and echocardiographic data were evaluated in a blinded manner in core laboratories.

Secondary efficacy and safety end points

By six months, median [IQR] NYHA class had improved from 3 [2-3] to 2 [2-3] ($p<0.001$), MLWHF score from 49±20 to 36±23 ($p<0.0001$), 6 minute walk distance from 313±105 to 345±106 metres, $p=0.0023$) and supine exercise duration at the time of right heart catheterisation from 7.3±3.1 to 8.2±3.4 minutes ($p=0.0275$; Figure 2).

At the 6 month follow up evaluation, there was a modest but significant increase in cardiac output at rest measured by thermodilution, consistent with increased right sided cardiac output due to the inter-atrial shunt (Figure 3). Oximetry was used to estimate left ventricular forward cardiac output at rest, which showed no change from baseline to follow-up (4.6±1.2 vs 4.8±1.3 L/min, $p=0.43$). The augmentation in thermodilution right-sided cardiac output during exercise was similar at baseline (rest vs exercise: 5.5±1.6 vs 8.7±2.6 L/min, $p<0.0001$) and 6 months (rest vs exercise: 6.7±1.5 vs 10.2±2.7 L/min, $p<0.0001$). Whilst resting PCWP was similar compared to the baseline study (17±5 vs 17±7mmHg, $p=0.24$), exercise PCWP was reduced, both at 20W (32±8 vs 29±9, $p=0.0124$) and at peak exercise (34±8 vs.32±8, $p=0.0255$) (Figure 3). At peak exertion, PCWP normalised for workload was lower at follow-up compared to baseline (69±40 vs 84±45 mmHg/Watt/kg, $p=0.0001$). There was no change in pulmonary vascular resistance (baseline vs. 6 months: 1.3±0.3 vs. 1.1±0.2 Wood units, $p=0.36$). Right atrial pressure was higher at follow-up than at baseline (9±4 vs. 11±5 mmHg, $p=0.0270$). At baseline the gradient between PCWP and RA was 8±4 mmHg, which fell to 6±3 mmHg at 6 months post IASD implantation ($p<0.0001$). Similarly, at peak exercise the gradient between PCWP and RA was 17±8 mmHg and this fell to 12±6 mmHg at 6 months post IASD implantation ($p=0.0002$).Consistent with the echocardiographic evaluation of device patency, measurement of oxygen saturations during cardiac catheterization confirmed a rise in pulmonary artery oxygen

saturation from 69±6 to 75±5% (p<0.0001) with a left-to-right shunt (pulmonary/systemic flow at baseline vs. 6 months: 1.06±0.32 6 months vs. 1.27±0.20; p=0.0004).

Echocardiography demonstrated small changes in chamber volumes at follow-up compared to baseline. The LV diastolic volume index decreased from 68±13 to 62±17 ml/m^2 (p=0.004) whilst the right ventricular end diastolic volume index increased from 22±9 to 27±11 ml/m^2 (p<0.001). The RA volume index increased from baseline to follow-up: 35±17 vs 40±22 ml/m^2 (p=0.014) whilst the LA volume index (34±17 vs 35±22 ml/m^2 was unchanged. Tricuspid annular plane systolic excursion (TAPSE) was also unchanged (20±4 vs. 20±4 mm).

Compared with baseline, there was a small reduction in body weight (90.1±18.3 to 88.4±18.6 kg/m^2, p=0.008). Neither NT-proBNP (median, IQR; 377 (222-925) vs. 382 (170-1075) pg/mL) nor eGFR (62±21 vs 61±20 ml/min/m^2) changed during the study. In the 6 months prior to trial participation, 20% (13/64) of patients required hospitalization for heart failure compared to 14% (9/63) in the 6 months subsequent to enrolment. The median dose of frusemide at baseline was 35mg/day (IQR 12.5 – 92.5). At 6 months the median dose was 35 mg/day (IQR 12.5 – 180), however the difference between groups was significant (by paired sign rank test, p=0.0176). The median difference in frusemide dose between 6 months and baseline was 0mg (IQR: 0 – 15mg/d), and only 7 patients had an increase in their diuretic dose. Because the difference was small, it is unlikely that a change in dose accounted for the observed effects.

Discussion

In this open-label study of a novel trans-catheter interatrial shunt device, developed for the management of patients with HFPEF, we observed reductions in left atrial pressure during exercise with improvements in functional capacity and quality of life 6 months after implantation. The procedure was well tolerated, and echocardiographic and oximetric studies demonstrated the presence of continuing device patency and left to right shunting at 6 months.

HFPEF is characterized by complex cardiovascular pathophysiology. Originally, attention focussed on the role of diastolic dysfunction [11,12] as a cause of a rapid rise in left ventricular diastolic and left atrial pressure during exertion. The underlying myocardial biology of HFPEF is controversial. It has been ascribed to myocardial fibrosis [17], myocyte hypertrophy and altered post-translation modification of myocardial proteins such as titin [18,19]. Additionally, many other factors contribute to the clinical profile of HFPEF patients, including hypertension [4,6] myocardial and systemic microvascular dysfunction [20,21] and left ventricular long-axis systolic dysfunction [22], as well as extra-cardiac co-morbidities such as renal insufficiency [23], anaemia, obesity and sleep apnoea [24].

To date, pharmacological management of HFPEF has not reduced morbidity and mortality. Even the impact of pharmacological therapy on symptoms or exercise capacity is uncertain. Therapeutic failure may reflect both diagnostic uncertainty and the complexity of the disorder. Identifying a homogenous patient population has also been challenging in HFPEF [25]. In the current study, we used invasive hemodynamic assessment both at rest and during exertion to identify, reliably, patients with objective evidence of impaired diastolic reserve. The use of exercise PCWP as a study end-point has only been reported once previously to assess the effectiveness of an intervention in HFPEF patients [26], although this is clearly relevant given the dynamic nature of the physiologic abnormality in HFPEF [11,12].

The current study was an open-label non-randomised study, thus we are unable to exclude a placebo effect. However, reduction in exercise pulmonary capillary wedge pressure is consistent with atrial decompression and the reduction in left ventricular end diastolic volume consistent with LV decompression. Peak exercise PCWP was reduced following shunt implantation despite an increase in exercise capacity and accordingly, PCWP normalized to workload, a measurement that has

predicted mortality in patients with HFPEF [13], was reduced. Left atrial decompression should lead to a reduction in left atrial volumes but this may have been attenuated by the increased venous return to the left atrium due to the shunt flow. Alternatively, the observation period may have been too short or a larger sample size may be required to detect changes, particularly in the setting of chronic atrial remodelling and atrial fibrillation. There were small increases in right atrial pressure and volume and right ventricular volume which may represent the effect of shunting per se or an increase in circulating volume. The latter possibility is unlikely as body weight fell during the study period. There was a modest increase in right sided cardiac output consistent with volume loading, whilst left sided output, as measured from oximetric observations was unchanged. The long-term sequelae of modest increases in right ventricular output are not known and therefore we excluded patients with significant right ventricular dysfunction.

Current guidelines for the diagnosis of HFPEF include evidence of elevated natriuretic peptides and echocardiographic measures of elevated filling pressures, as reflected by the E/e' ratio [27]. In this study, device implantation was not accompanied by reduction in either of these non-invasive measurements. This finding may be explained by the fact that these measures were conducted at rest or by the relatively modest overall reduction in filling pressures.

Taken together the current open-label non-randomized study demonstrates that trans-catheter trans-venous placement of an interatrial shunt device is feasible and may be associated with improvements in exercise haemodynamics, functional capacity and quality of life. These findings require validation in a randomized controlled blinded study.

Author Contribution: GH, DB, FES, JGFC, MP, ML and DK contributed to the analysis of data and preparation of the manuscript. CH, SM, JVH, FM , DK and IL contributed to data collection.

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FIGURE LEGENDS

Figure 1. Schematic diagram of interatrial septal device (IASD) allowing communication between left and right atria (left panel) and echocardiographic image demonstrating Doppler colour flow from left to right atrium (right panel).

Figure 2. Bar graphs showing New York Heart Association Class, Minnesota Living with Heart Failure score, six minute walk test distance and exercise time during right heart catheterisation at baseline and follow-up.

Figure 3. Bar graphs showing cardiac output and pulmonary capillary wedge pressure (PCWP) at rest and exercise at baseline and follow-up. PCWP normalized to workload is also presented.

Table 1. Patient characteristics at baseline

Variable	
Age (years)	69±8
Gender (n, M/F)	22/42
NYHA Class (n, II/III/IV)	18/46/0
BMI, kg/m^2	33±6
eGFR (ml/min/1.73m^2)	62±21
Haemoglobin (g/L)	133±5
Co-Morbidities n(%)	
Diabetes	21 (33)
Hypertension	52 (81)
Atrial fibrillation	23 (36)
CAD	23 (36)
Echocardiography	
LV end diastolic volume index (ml/m^2)	68±13
LVEF (%)	47±7
LV mass index (g/m^2)	119±36
LA diastolic volume index (ml/m^2)	34±17
RV diastolic volume index (ml/m^2)	22±9
RA volume index (ml/m^2)	35±17
E/A ratio	1.3±0.8
E/e' ratio	13.9±5.9
TAPSE (mm)	20±4
NT-Pro BNP (pg/mL)*	377 (222-925)
Resting Haemodynamics	
Mean RA Pressure (mmHg)	9±4
Mean PA Pressure (mmHg)	25±7
Mean PCWP (mmHg)	17±5
Cardiac output (L/min)	5.5±1.6

Data are mean±standard deviation, except *NT-BNP (median, IQR).

467 Figure 1
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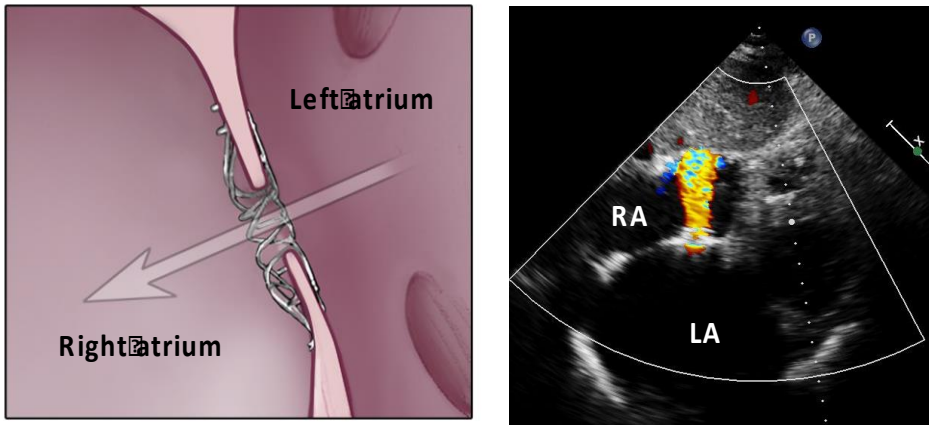

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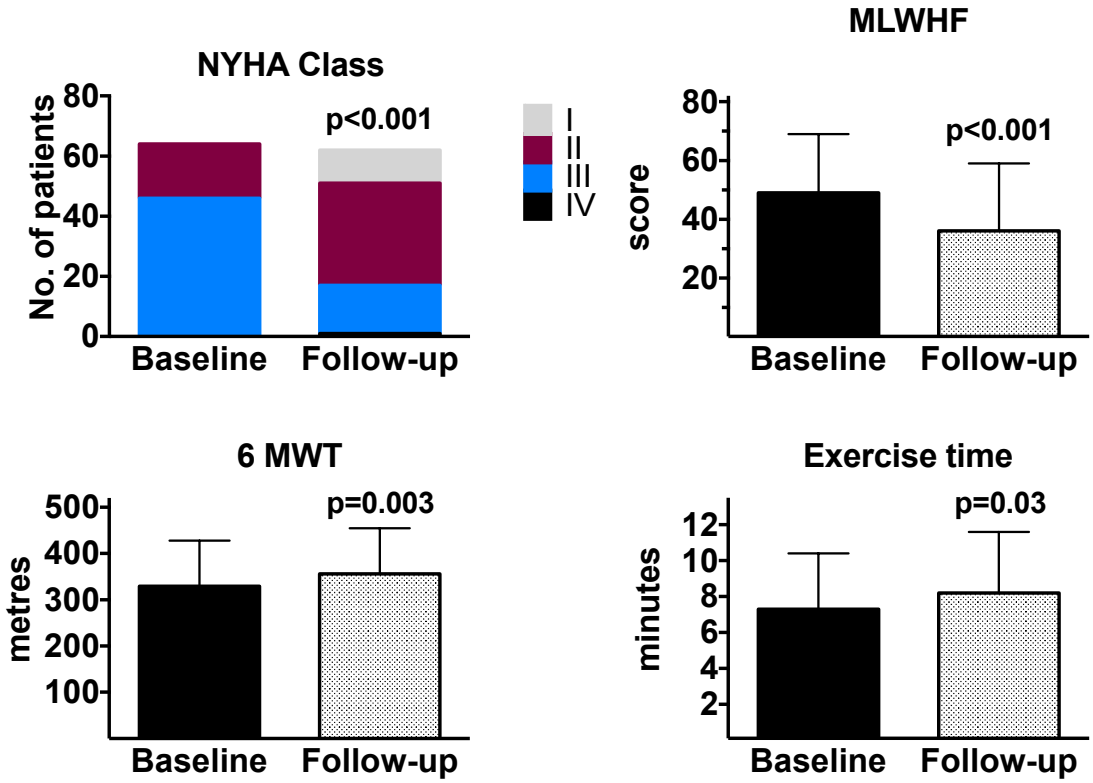
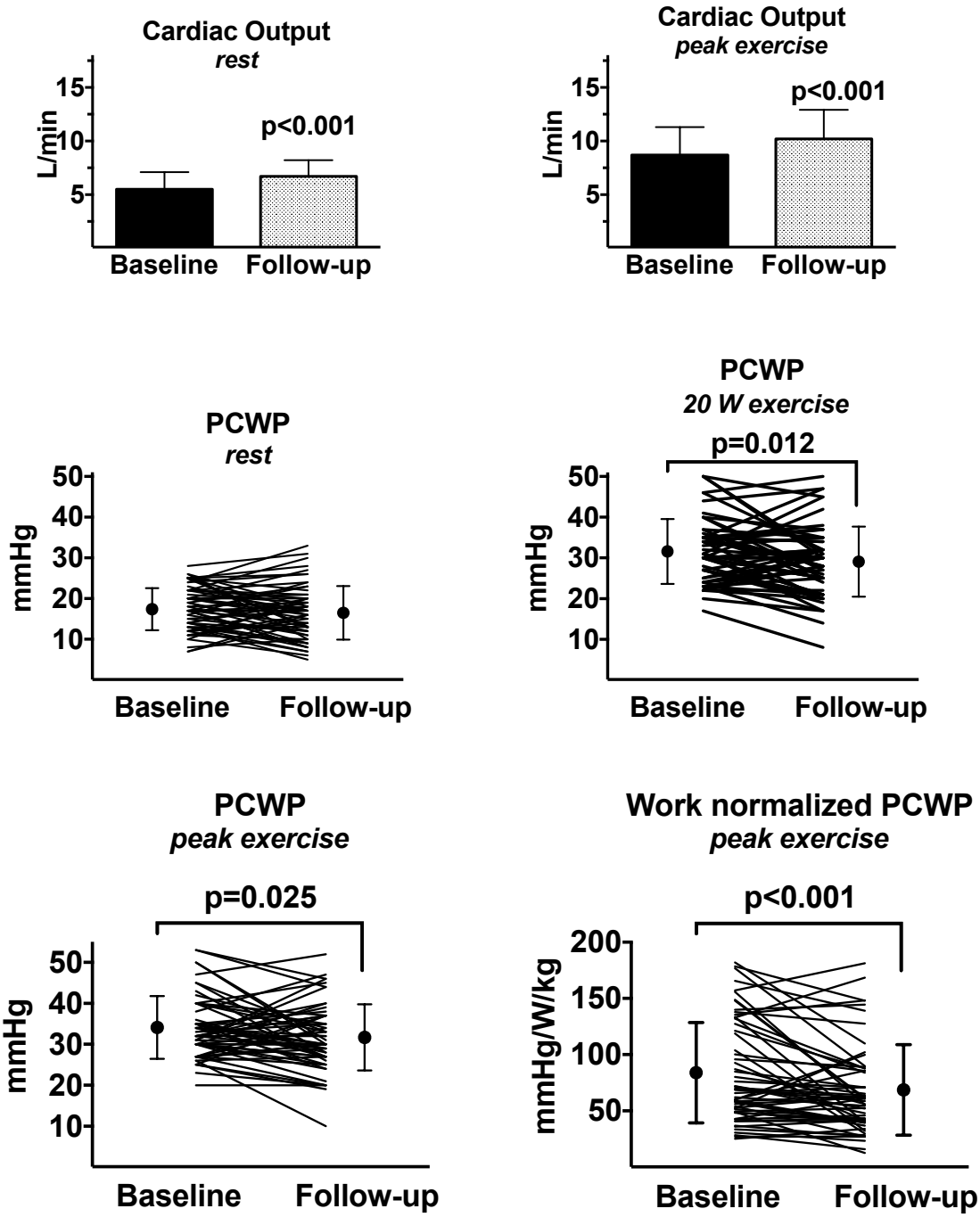
Figure 2


NYHA Class
No. of patients
80
60
40
20
0
p<0.001
Baseline
Follow-up
I
II
III
IV
MLWHF
score
80
60
40
20
p<0.001
Baseline
Follow-up
6 MWT
metres
500
400
300
200
100
p=0.003
Baseline
Follow-up
Exercise time
minutes
12
10
8
6
4
2
p=0.03
Baseline
Follow-up

474 Figure 3
475



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Author's Statement:

All authors have read and approved the submission of the final draft of the manuscript.

All authors contributed to the acquisition and/or analysis of the study data.

Members of the study steering committee (GH, MCP, JGFC, ML and DMK) prepared the manuscript.

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REDUCE LAP-HF study investigators

Gerd Hasenfuβ, MD, Chris Hayward MD, Dan Burkhoff, MD, Frank E. Silvestry, MD, David Muller, MD Scott McKenzie, MD, Darren Walters, MD Filip Malek, MD, Petr Neuzil, MD, Jan Van der Heyden, MD, Marco C Post, MD, Antony S Walton, MD, Irene Lang, MD, Rob Doughty, MD, Peter Ruygrok, MD, Jean-Noël Trochu, MD, Patrice Guerin, MD, Finn Gustafsson, MD, Lars Søndergaard, MD, Adam Kolodziej, MD, Ralf Westenfeld, MD, Martin Penicka, MD, Jozef Bartunek, MD Mark Rosenberg, MD, Jörg Hausleiter, MD, Philip Raake, MD, Raffi Bekeredjian, MD, Mark C Petrie, MD, Niki Walker, MBChB, Guillaume Jondeau, MD, Gregory Ducrocq, MD, Martin Bergmann, MD, John GF Cleland, MD, Martin Leon, MD and David M Kaye MD*

Affiliations:

Gerd Hasenfuβ, MD, Georg-August Universität, Gottingen, Germany; Chris Hayward MD, St Vincent Hospital, Sydney, Australia; Dan Burkhoff, MD, MD, PhD, Columbia University, New York, NY, USA; Frank Silvestry, MD, Hospital of the University of Pennsylvania, Philadelphia PA, USA; David Muller, MD St Vincent Hospital, Sydney, Australia; Scott McKenzie, MD, The Prince Charles Hospital, Brisbane, Australia; Darren Walters, MD, The Prince Charles Hospital, Brisbane, Australia; Filip Malek, MD, Na Homolce Hospital, Prague, Czech Republic; Petr Neuzil, MD, Na Homolce Hospital, Prague, Czech Republic; Jan Van der Heyden, MD, St Antonius Ziekenhuis, Nieuwegein, The Netherlands; Marco Post, MD, St Antonius Ziekenhuis, Nieuwegein, The Netherlands; Antony S Walton, MD, Alfred Hospital, Melbourne, Australia; Irene Lang, MD, Allgemeines Krankenhaus Universitätskliniken, Vienna, Austria; Rob Doughty, MD, University of Auckland, Auckland, New Zealand; Peter Ruygrok, MD, Auckland City Hospital, Auckland, New Zealand; Jean-Noël Trochu, MD, CHU de Nantes, Nantes, France; Patrice Guerin, MD, CHU de Nantes, Nantes, France; Finn Gustafsson, MD, Department of Cardiology, Rigshospitalet, Copenhagen, Denmark; Lars Søndergaard, MD, Department of Cardiology, Rigshospitalet, Copenhagen, Denmark; Adam Kolodziej, MD, Fourth Military Hospital, Wroclaw, Poland; Ralf Westenfeld, MD, Universitätklinikum Dusseldorf, Dusseldorf, Germany; Martin Penicka, MD, Onze Lieve Vrouwen Ziekenhuis, Aalst, Aalst, Belgium; Jozef Bartunek, MD, Onze Lieve Vrouwen Ziekenhuis, Aalst, Aalst, Belgium; Mark Rosenberg, MD, Universtitaätklinikum Schlewig Holstein, Kiel, Germany; Jörg Hausleiter, MD, Klinikum der Universität Munchen, Munich, Germany; Philip Raake, MD, University of Heidelberg, Heidelberg, Germany; Raffi Bekeredjian, MD, University of Heidelberg, Heidelberg, Germany; Mark C Petrie, MD, Golden Jubilee National Hospital, Glasgow, Scotland, Great Britain; Niki Walker, MD, Golden Jubilee National Hospital, Glasgow, Scotland, Great Britain; Guillaume Jondeau, MD, Bichat Hospital, Paris, France; Gregory Ducrocq, MD, Bichat Hospital, Paris, France; Martin Bergmann, Cardiologicum Hamburg, Hamburg, Germany; John GF Cleland, MD, National Heart & Lung Institute, Royal Brompton and Harefield Hospitals, Imperial College, London, Great Britain; Martin Leon, MD, Columbia University Medical Center, New York, NY, USA; David Kaye, MD, Alfred Hospital and Baker IDI Heart & Diabetes Institute Melbourne.